PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Elisabeth M. Bock, et al.	**Examiner:**	J. Andres
Serial No.:	09/781,509	**Art Unit:**	1646
Filed:	February 12, 2001	**Docket:**	12754A

For: NEUROGENIC COMPOSITIONS AND METHODS

Commissioner for Patents
United States Patent and Trademark Office
Alexandria, Virginia 22313-1450

DECLARATION OF DR. EUGENE LUKANIDIN UNDER 37 C.F.R. §1.132

Sir:

I, Eugene Lukanidin, hereby declare as follows:

1. I am one of the co-inventors of the above-identified application.

2. I hold a Bachelor of Science (M.D.) Degree in 1966 and a Doctorate Degree in 1978. My research interest is in the field of Molecular and Cancer Biology, and I have authored more then 100 publications in this field. Currently I am a Professor at the Department of Molecular Cancer Biology, Institute of Cancer Biology, Danish Cancer Society. A true and correct copy of my curriculum vitae is attached hereto as Exhibit A.

3. I have reviewed the above-identified application (hereinafter referred to as '509 application), and I am familiar with the subject matter therein. Specifically, the '509 application provides the unique recognition that Mts1 proteins form multimers in physiological solutions and

that the neurogenic activity of Mts1 proteins is associated with the multimeric forms of the protein, as opposed to the monomeric and dimeric forms of the protein. Accordingly, the '509 application is directed to an isolated multimeric Mts1 protein complex which contain three or more molecules of an Mts1 protein.

4. I have also read the Final Action dated May 19, 2003, issued in the '509 application. It is my understanding that the Examiner holds the opinion that U.S. Patent No. 5,801,142 to Zain et al. ("the '142 patent") teaches an isolated trimeric form of human Mts-1. Specifically, referring to column 38, lines 50-52 and Figure 15 of the '142 patent, the Examiner states that the '142 patent teaches that the mouse Mts1 protein migrates on a gel with a molecular weight of 10-12 kD. Further referring to Figure 16 and column 38, lines 53-58 of the '142 patent, the Examiner states that the '142 patent also teaches that the human Mts1 protein has an apparent molecular weight of 27 kD. The Examiner reasons that, since there is a difference of only 7 amino acids between the mouse and human sequences, it appears that the 27 kD band identified in Figure 16 of the '142 patent represents a trimeric form of human Mts-1.

5. I have reviewed the '142 patent in its entirety. It is my scientific opinion that the '142 patent does not teach an isolated trimeric form, or any other multimeric form, of Mts-1, as disclosed and claimed in the '509 application.

6. The experiment underlying Figure 16 of the '142 patent is described at column 38, lines 6-13. Specifically, serum samples were obtained from normal women and patients with breast carcinomas or advanced malignant lymphomas. 150 μg of each serum sample was run on a 12% SDS-PAGE gel. The proteins were transferred to PVDF membranes and the membranes were probed with a 1:1000 dilution of α-mts1 and then with a 1:1000 dilution of the secondary antibody (rabbit anti-chicken IgG-HRP). The reaction was developed with a DAB solution. Figure 16 illustrates that a protein band with an apparent molecular weight of approximately 27 kD could be detected in serum from a patient with metastatic breast cancer as well as two patients with metastatic lymphomas, but not in serum from a normal patient or patients with non-

metastatic breast cancer or non-metastatic lymphomas. The 27 kD band apparently contains denatured human Mts1 polypeptide, as the band was detected by α-mts1 antibodies and disappeared (i.e., competed off) when the Western blot was probed with α-mts1 antibodies in the presence of free mts-1 protein. See column 38, lines 64-67 of the '142 patent.

7. It is my scientific opinion that, because the serum samples were run on a 12% SDS-PAGE gel, the 27 kD band in Figure 16 of the '142 patent merely represents an aggregate of denatured proteins. The aggregate could be an aggregate containing one or more denatured Mts1 polypeptides, or an aggregate containing a denatured Mts1 polypeptide and other polypeptides present in the serum sample. In contrast to an aggregate of denatured polypeptides of the '142 patent, the multimeric Mts1 complex, as disclosed and claimed in the '509 application, is composed of undenatured Mts1 proteins and has neurogenic activity. In addition, the multimeric Mts1 complex, as disclosed and claimed in the '509 application, appears as an 11 kD band on an SDS-PAGE (i.e., under denaturing conditions). See Figure 11D and page 37, lines 25-30 of the '509 application.

8. It is also my scientific opinion that, regardless of the nature of the 27 kD band, one skilled in the art would not consider the Western blot analysis depicted in Figure 16 of the '142 patent to be an isolation or purification of the 27 kD polypeptide. As described in the '142 patent, human serum samples were run on the SDS-PAGE before the Western blot analysis. The 27 kD band, which apparently contained human Mts1, was merely <u>detected</u> as a component among numerous proteins present in the serum sample. In this instance, the SDS-PAGE coupled with the Western blot analysis, was merely a procedure for detection of the Mts1 material. There was simply <u>no recovery</u> of the 27 kD material, i.e., <u>no isolation</u> of the 27 kD material, away from other components in the serum sample. In contrast, the multimeric Mts-1 complex, as disclosed and claimed in the '509 application, is in an <u>isolated</u> form, and can be isolated by an appropriate chromatography procedure, as exemplified in Example 3, the paragraph bridging pages 36-37 of the '509 application.

9. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: Eugene Lukanidin

Dated: 17/09/03

CURRICULUM VITAE

Name: Eugene M. Lukanidin
Title: Professor, Ph.D., M.D.
Date of Birth: May 14, 1942
Place of Birth: Kuybishev, USSR
Nationality: Russian

Address: Danish Cancer Society,
Institute of Cancer Biology,
Dept. of Molecular Cancer Biology,
Strandboulevarden 49, opg. 4.3.
DK-2100 Copenhagen, Denmark
Telephone: +45 35 25 73 13
Fax: +45 35 25 77 21
E-mail: el@cancer.dk

Affiliation position: Head of Department, (Dept. of Molecular Cancer Biology), Institute of Cancer Biology, Danish Cancer Society.
Member of Russian Academy of Natural Sciences, Moscow 1991.

Education:
1966 M.D. - Medicine. Second Moscow Medical Institute of Medicine.

1969 Ph.D. - Biology/Mol.Biol. Institute of Molecular Biology, Moscow.

1978 D.Sc. - Biology/Mol.Biol. Institute of Molecular Biology, Moscow.

Professional experience:
1966 - 1969 Postgraduate Student, Institute of Molecular Biology, Moscow.
1969 - 1976 Junior Scientist, Institute of Molecular Biology, Moscow.
1976 - 1983 Senior Scientist, Institute of Molecular Biology, Moscow.
1983 - 1990 Leading Scientist, Institute of Molecular Biology.
1990 - 1992 Head of the Laboratory of Molecular Genetics of Cancer, Institute of Gene Biology, Moscow.
1992 - present Head of Department of Molecular Cancer Biology, Institute of Cancer Biology, Danish Cancer Society, Copenhagen.

Fellowships:
1968 - 1969 The Norwegian Institute for Cancer Research - Visiting Scientist (Laboratory of Biochemistry - Dr. A. Phil).

1975 - 1976 Cold Spring Harbor Laboratory - Visiting Scientist (Laboratory of DNA Tumor Viruses - Dr. J. Sambrook).

1983 M.I.T. Cancer Research Center - Visiting Scientist (Laboratory of Molecular Oncology - Dr. R. Weinberg).

Eugene Lukanidin: List of publications 1967 - 2003:

(Only papers published in English)

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